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Morscher, Raphael Johannes ; Rauscher, Christian ; Sperl, Wolfgang ; Rittinger, Olaf

DOI: https://doi.org/10.1016/j.seizure.2017.06.017

Seizure 50 (2017) 118–120

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Clinical letter

Seizures, enamel defects and psychomotor developmental delay: The first patient with Kohlschütter-Tönz syndrome caused by a *ROGDI*-gene deletion

Raphael Johannes Morscher[a,b,*], Christian Rauscher[a], Wolfgang Sperl[a], Olaf Rittinger[a]

[a] Division of Clinical Genetics, Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria
[b] Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria

ARTICLE INFO

Article history:
Received 17 July 2016
Accepted 13 June 2017

Keywords:
Kohlschütter-Tönz syndrome
Infantile seizure onset
Psychomotor developmental delay
Enamel defect
ROGDI-gene deletion

1. Background

Up to 70% of epilepsies have been reported to be related to genetic factors with a continuously enlarging fraction known to be caused by monogenetic alterations [3]. Even with the advent of massive parallel sequencing, the recognition of classical epilepsy-syndromes can be key to rapid diagnosis, which can guide therapy and provide valuable information on prognosis. This report emphasizes key features of Kohlschütter-Tönz Syndrome (KTS), a clinically recognizable cause of epilepsy caused by biallelic mutations in the *ROGDI*-gene.

2. Case report

At the age of seven months, a baby boy was referred to the neuropediatric outpatient unit because of developmental delay. He was born as the third son to a non-consanguineous Caucasian couple. Pregnancy was uneventful with good adaption after birth at 38 + 5 weeks. Birth parameters were normal. Mild hip dysplasia was treated with a Pavlik-bandage.

Evaluation showed peripheral and truncal hypotonia (video 1 in Supplementary material) with symmetric movements and normal reflex patterns. Speech was delayed with vowel sounds only. Fine jerk nystagmus (video 2 in Supplementary material) and reduced fixation time were present on ophthalmologic examination. Ocular fundus exam was repeatedly normal with no indication of optic atrophy. Cranial ultrasound was normal. Pectus excavatum and joint hypermobility (Supplemental Fig. 1A and B) were noted. No other dysmorphic features were present. The boy was exclusively breast fed until this time [H 72 cm (P 90), HC 45 cm (P 50–75) and BW 6.6 kg (P 50–75)].

At the age of nine months a self-limiting, fever-induced seizure occurred. The patient was atonic with eyes turned and perioral cyanosis. He was initially started on valproic acid. Because of treatment resistance, therapy was changed to levetiracetam at the age of 16 month with persistent treatment success and less than one clinically manifest seizure yearly (current cdosing: 43 mg/kg). The remaining seizures were most likely linked to repeated parental cessation of drug application and showed focal tonic-clonic aspects with secondary generalization.

After the age of 1.5 years, the patient progressively developed a dystrophic aspect stabilizing at around P 3–10 for H and HC but with a BW below P3. With two years, uniform yellow discoloration and carious changes of front teeth were first noted. As seen in Fig. 1C/D and S1E (4.5 and 6.8 years), more severe changes of maxillary incisors and canines were present that showed early progression to complete enamel loss and brownish-black discoloration. These teeth were extracted at 5.5 years.

Abbreviations: KTS, Kohlschütter-Tönz syndrome; H, hight; HC, head circumference; BW, body weight; EEG, electroencephalogram.

* Corresponding author at: Universitätsklinik für Kinder– und Jugendheilkunde der Paracelsus Medizinischen Privatuniversität. Müllner Hauptstraße 48, 5020 Salzburg, Austria.
E-mail address: raphael.morscher@pmu.ac.at (R.J. Morscher).

http://dx.doi.org/10.1016/j.seizure.2017.06.017

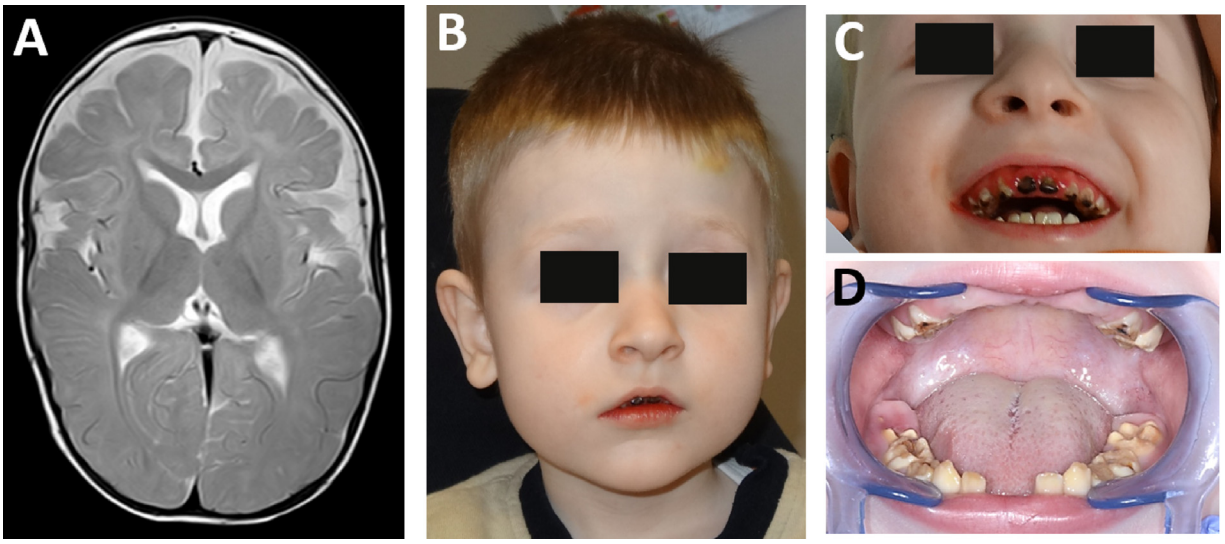

Fig. 1. A) T2 wted MRI at the age of 10 month. Results were widely normal with no structural malformations. Slight widening of external liquor spaces and discrete left frontoparietal parenchymal rarefication were noted. B) Facial gestalt showed hypotonic impression without overt dysmorphic features. C and D) Enamel defects at 5.5 and 6.8 years respectively.

Even after cessation of seizures, psychomotor development continued to be significantly delayed and was dominated by persistent proximal and distal hypotonia. The patient started rolling over at two years; unaided sitting (video 3 in Supplementary material) and crawling started at 3.5 years; with 4 years he learned to eat and stand with support. Playing ball is one of the favorite activities (video 4 in Supplementary material). No progressive neurodegenerative or myopathic aspects to the disease were noted on neurological examination. Nystagmus persisted; eye contact and targeted grasps were possible (video 5 in Supplementary material). Babbling was present with three years and single words identifying family members with 5.5 years. No active speech was acquired until the last follow up at 6.8 years.

3. Investigations

EEG at time of first seizure (nine months) showed normal background activity with a partially steep and irregularly configured right-sided temporal theta-delta-focus. Additionally fronto-central spike-groups were detected. At 6.8 years follow up EEG showed a right-sided temporal sharp-wave focus with generalized low background activity. MRI was widely normal with no structural malformations. Slight widening of external liquor spaces and discrete left frontoparietal parenchymal rarefication were noted (Fig. 1A). Stable findings were confirmed at the age of 21 months. Echocardiography was normal. Metabolic screening including plasma amino acids, ammonia, acylcarnitine profile, urine organic acids and transferrin isoelectric focusing was normal.

Throughout the years, laboratory analysis showed mild hepathopathy with intermittently elevated ALT/AST <100 U/l, LDH 300–350 U/l and GGT <100 U/l levels. On ultrasound, increased liver density was noted consistent with diffuse parenchymal damage without focal lesions. Genetic testing revealed the rare *SERPINA1* genotype PiPZ and therefore alpha 1-antitrypsin deficiency as a potential cause.

Initial genetic evaluation for epilepsy included *SCN1A* sequencing and FISH subtelomere screen. Subsequently SNP-array diagnostics was conducted according to the manufacturer's instructions (CytoScan® HD, Affymetrix; Chromosome Analysis Suite (ChAS) Software). Array results showed an initially unclassified 64 kb deletion distal to the *ROGDI*-gene (Fig. 2A). This region

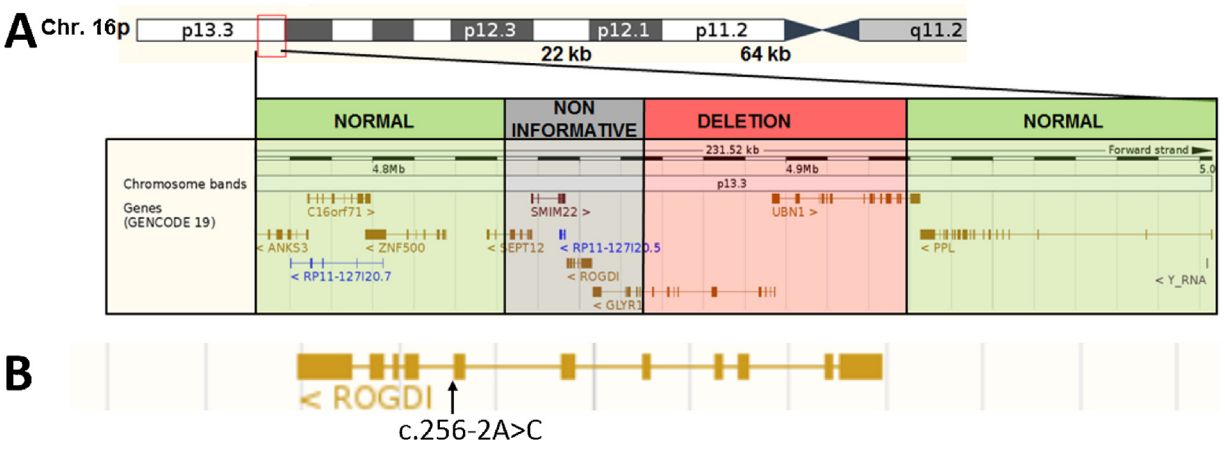

Fig. 2. A) P-arm of chromosome 16 (overview) with the ROGDI-gene region in detail. Shaded in green are proximal and distal regions with normal copy number on CytoScan® HD analysis. 64 kb deletion (red) and not covered region (grey) includes the ROGDI-gene locus. B) ROGDI-gene structure and mutation c.256–2A > C (NM_024589.1) on paternal allele. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

includes parts of *GLYR1* and *UBN1*, two genes with no OMIM phenotype described (hg19/GRCh37:Chr16:4,864,100-4,928,339).

Supported by the dental phenotype of yellow discoloration with severe carious defects, Sanger sequencing of the *ROGDI*-gene, mutated in Kohlschütter-Tönz syndrome (OMIM #226750), was performed. This test revealed an apparently homozygous splice site mutation c.256–2A > C (NM_024589.1). Upon parental evaluation, only the father tested positive for this mutation. Re-evaluation of the array results showed that the described deletion on chromosome 16p extends into the *ROGDI*-gene region, which is not covered by the CytoScan® HD chip and was therefore initially not reported. This is the first description of a compound heterozygous patient with a *ROGDI*-gene deletion on one allele and KTS (Fig. 2A/B). Variants were absent from publicly available genome-variant databases.

4. Discussion

KTS is an autosomal recessive monogenic cause of epilepsy that can be clinically recognized due to its distinct combination of cardinal symptoms. Main characteristics are early onset epilepsy (often treatment resistant), enamel defects, developmental delay and verbal deficiency. Although phenotypic variability has been reported, intellectual disability is mostly severe with both gross and fine motor skills being severely impaired. Nystagmus and non-specific dysmorphic features such as pectus excavatum have been reported [1,2,4]. Despite the description of *ROGDI*-mutations as an underlying cause of KTS in 2012, the pathophysiological mechanism remains elusive [2]. It is thought that the strictly postnatal CNS phenotype might be reflective of the increased cerebral ROGDI-protein expression in this time period.

In all KTS patients described, the first epileptic seizures occurred before the age of three years and often proofed difficult to treat [1,2,4]. No classic EEG or seizure patterns for KTS exist. Even though severity of epileptic activity seems to reflect the degree of neurocognitive involvement, seizure control did not improve prognosis in responsive cases. For the majority of reported cases, developmental regression has been described following seizure onset, rendering affected patients in an immobile and nonverbal state in late adolescence/early adulthood. At this stage, clinically evident seizure frequency significantly decreases independent of treatment.

The presented patient showed an atypically mild course of epilepsy that could be managed by levetiracetam. It can be speculated that the combination of a gene deletion and a splice-mutation underlies this less severe phenotype. Especially the yellow-brown discoloration immediately after teething, which affects primary as well as permanent teeth, has high recall value. With limited exceptions such as oculo-dento-digital dysplasia and tuberous sclerosis, current differential diagnosis of amelogenesis imperfecta are neither combined with epilepsy nor developmental delay. Also in our case, the tooth phenotype in combination with epilepsy was the key to clinical diagnosis.

Conflict of interest

Morscher, Raphael Johannes; Rauscher, Christian; Sperl, Wolfgang; Rittinger, Olaf: We have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2017.06.017.

References

[1] Mory A, Dagan E, Shahor I, Mandel H, Illi B, Zolotushko J, et al. Kohlschutter-Tonz syndrome: clinical and genetic insights gained from 16 cases deriving from a close-knit village in Northern Israel. Pediatr Neurol 2014;50(4):421–6.
[2] Schossig A, Wolf NI, Fischer C, Fischer M, Stocker G, Pabinger S, et al. Mutations in ROGDI cause Kohlschutter-Tonz syndrome. Am J Hum Genet 2012;90(4):701–7.
[3] Thomas RH, Berkovic SF. The hidden genetics of epilepsy-a clinically important new paradigm. Nat Rev Neurol 2014;10(5):283–92.
[4] Tucci A, Kara E, Schossig A, Wolf NI, Plagnol V, Fawcett K, et al. Kohlschutter-Tonz syndrome: mutations in ROGDI and evidence of genetic heterogeneity. Hum Mutat 2013;34(2):296–300.